UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/817,248	04/02/2004	Sherin S. Abdel-Meguid	50201/003002	3934

21559 7590 05/04/2006

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
KOSAR, ANDREW D	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 05/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/817,248	ABDEL-MEGUID ET AL.	
	Examiner	Art Unit	
	Andrew D. Kosar	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *102 and 104-109* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *102 and 104-109* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment / Arguments

Claim 102 and new claims 104-109 are pending. Claims 1-101 and 103 have been cancelled.

Applicant's arguments filed March 31, 2006 have been considered.

Any rejection and/or objection not specifically addressed is herein withdrawn.

Information Disclosure Statement

The information disclosure statement filed March 31, 2006 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because:

(A) Applicant has not provided legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed; and

(B) Applicant has not provided a proper IDS which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement.

It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement

or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Because Applicant has not provided sufficient information, the Examiner is unable to determine if the statement provides evidence of applicable art under 35 USC §§ 102 and/or 103(a).

Specification

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:
Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 102 and 104-109 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The instantly claimed Factor XI proteins and fragments are research tools for designing and determining inhibitors of Factor XI (e.g. Abstract, throughout), stating that, "In desirable embodiments, the mutation(s) allow crystallization or increase the resolution of the corresponding three-dimensional structure of the mutant protein compared to the structure of Factor XI without the mutation(s). For example, the mutations may increase the size or order of the resulting crystals, resulting in a higher

resolution structure." (US 2005/0143317 A1 (PGPUB of instant Application), paragraphs [0100] and [0245]).

Further, the specification teaches that, "to facilitate the identification and/or design of high affinity inhibitors for Factor XIa, several three-dimensional structures of the human Factor XI catalytic domain (FXIcat) bound to a ligand have been determined (FIGS. 3, 4A, 4B, 5A, 5B, 5C, 5D, and 12-16). These structures can be used to homology model the structure of other candidate inhibitors with FXIcat. In addition, the methods described herein for the crystallization and structural determination of complexes of FXIcat with a ligand can be used to experimentally determine the structure of other ligands bound to FXIcat. This structural information can be used to identify functional groups within a ligand that can be modified to increase the affinity and selectivity of the ligand for Factor XIa or to identify functional groups within the ligand that can be modified to increase the bioavailability of the ligand without adversely affecting its affinity for Factor XIa." (paragraph [0239]). It is noted that the specifically recited mutations within the claims are within the catalytic domain.

In the instant case, the utility is a 'general utility', as the MPEP states that the following categories are not substantial utilities: (A) Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved; (B) A method of treating an unspecified disease or condition; (C) A method of assaying for or identifying a material that itself has no specific and/or substantial utility; (D) A method of making a material that itself has no specific, substantial, and credible utility; and (E) A claim to an intermediate product for use in making a final product that has no specific, substantial and credible utility. MPEP § 2107.01(I).

Further, with regards to research tools, the MPEP states, "An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention." MPEP § 2107.01(I).

Claim Rejections - 35 USC § 112

> The following is a quotation of the first paragraph of 35 U.S.C. 112:
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 102 and 104-109 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 104-109 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, no that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus (MPEP § 2163). If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus (*See* MPEP § 2163). Although the MPEP does not define what constitute a

sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The factors considered in the Written Description requirement are (1) *level of skill and knowledge in the art*, (2) *partial structure*, (3) *physical and/or chemical properties*, (4) *functional characteristics alone or coupled with a known or disclosed correlation between structure and function*, and the (5) *method of making the claimed invention.*

In the instant case, the claims are drawn to a myriad of mutant Factor XI proteins or fragments, wherein the mutation is a) a mutation of a residue that disrupts post-translational N-linked glcosylation, b) a mutation that eliminates a free, reactive sulfhydryl group of a cysteine, or c) an N- or C- terminal residue mutation that promotes crystallization relative to the native (nonmutated).

(1) Level of skill and knowledge in the art:

The level of skill and knowledge in the art have been discussed previously (see Office Action mailed 8/5/05, pages 6-8), and are low with respect to the effect of knowing what effect substitutions have on proteins.

(2) Partial structure:

The claims provide that the product is a mutant of Factor XI (FXI). The specification provides for 'alanine screening' mutants at S434 (S434A) and T475 (T475A), each alone or in combination with the other. Additionally, the specification provides for the S434/T475 mutation in combination with the following mutations: K422A, K437A, K486A, K505A, and K509A, as well as AVC-terminal truncation; and

S434A/T475A with C482S, alone or in combination with K437A, R479A, K505A, D476A, and Y416S.

The specific structure of FXI is not described in the claims, e.g.- human, mouse, or rat, by a specific sequence. The specification provides three sequences of FXI from only three different sources: Homo sapiens (Human), Oryctolagus cuniculus (European Rabbit), and Mus musculus (mouse).

The specification and claims lack sufficient number and variety in the type of mutation(s) and sequences of FXI to sufficiently describe the genus.

(3) Physical and/or chemical properties and (4) functional characteristics:

The compound is FXI or a fragment with mutations that promote crystallization relative to the native form or disrupt post-translationally N-linked glycosylation when recombinantly expressed. The specification provide that the mutation a) enhances crystallization of the catalytic domain, b) is "a mutation of a residue that is otherwise post-translationally modified in an organism used for recombinant expression", c) alters the charge, d) eliminates a free, reactive sulfhydryl of a cysteine, e) alters the charge density without altering the overall charge, f) is an N- or C- terminal residue mutation, or g) alters the folding.

The specification lacks sufficient description of all mutations which would have the asserted function, and does not provide sufficient variance in the genus to fully describe the myriad of mutations and fragments with mutations which are embraced by the generic.

(5) Method of making the claimed invention:

Methods of making proteins and peptide fragments are well known in the art, e.g. Merrifield peptide synthesis and recombinant methods.

The specification does not provide sufficient description on how one would make mutants with the asserted functions, e.g. a mutation that promotes crystallization of FXI or a fragment thereof, providing only specific point mutations. Further the specification only provides description for a limited number of amino acid substitutions, but does not describe the myriad of 'mutations' embraced by the generic that would have the asserted function.

As stated *supra*, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claims 104-109 are broad generic claims, with respect to all possible FXI mutant proteins and fragments encompassed by the claims. The possible structural variations are limitless to any class of FXI mutant protein or fragment. It must not be forgotten that the MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. Here, though the claims may recite some functional characteristics, e.g. 'a mutation that promotes crystallization' or 'disrupts post-translational N-linked glycosylation', the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect

this variance in the genus since the specification does not provide any examples of fragments with the asserted function. While having written description of the specific mutations claimed in claim 102 for FXI (SEQ ID NO:15) which has the specific starting amino acids, e.g. S434, T475, the specification is void of sufficient variety of specific mutations or a correlation between the mutation(s) and the desired function.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 105, 107 and 108 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 105 is indefinite because recites, "a human polypeptide sequence". It is unclear what constitutes 'a human polypeptide sequence', as compared to, e.g., a synthetic peptide, being they both have the same connectivity and spectroscopic results and would be indistinguishable one from the other by analytic techniques.

Claims 107 and 108 recite, "relative to the mature human Factor XI...", however it is unclear whether the protein or fragment of claims 104 (and/or 106) must be SEQ ID NO:15, or whether it can be any peptide so long as it has some amino acid which corresponds to said single point mutation(s). In the case of the latter, the claim is

indefinite because one would not be able to determine what peptides are, or are not, embraced by the claims.

Claim 108 recites, "... in said protein or fragment at position C482S..." and it is unclear whether the specific mutation required by claim 108 is C482S, or whether amino acid position 482 is mutated from S482 to another amino acid, e.g. S482T, S482Y, etc. and thus the claim is indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 104, 105 and 109 are rejected under 35 U.S.C. 102(b) as being anticipated by KONISHI (US Patent 4,461,724).

The instant claims are generally drawn to mutants of FXI.

Konishi teaches the tetrapeptide Leu-Ser-His-Lys (claim 7) which meets the limitations of being 'a fragment' of SEQ ID NO:15 where it has been mutated to eliminate a free reactive sulfhydryl. The sequence in SEQ ID NO:15 it corresponds to is Leu-Ser-Cys-Lys (aa 561-564).

Claims 104-106 and 109 are rejected under 35 U.S.C. 102(b) as being anticipated by SCHMID (US Patent 5,919,895).

Schmid teaches Val-Val-Tyr-Thr-Asp (SEQ ID NO:3), which corresponds to a mutant of Val-Asn-Tyr-Thr-Asp (aa 472-476), which 'disrupts' N-glycosylation. The pentapeptide inherently is missing the terminal amino acids at positions 606 and 607.

Claims 102, 104, 105 and 109 are rejected under 35 U.S.C. 102(b) as being anticipated by PENNING (T.M. Penning, et al. J. Biol. Chem. (1982) 257(21), pages 12589-12593).

Penning teaches Tyr-Ala-Asp-Ser (compound III, page 12590), which is considered to be a fragment of SEQ ID NO:15 which has been mutated T475A (corresponding to Tyr-Thr-Asp-Ser, aa 474-477). The tetrapeptide inherently is missing the terminal amino acids at positions 606 and 607.

Claim 102, 104, 105, 107 and 109 are rejected under 35 U.S.C. 102(b) as being anticipated by STROMINGER (J.L. Strominger, et al. J. Am. Chem. Soc. (1959) 81, pages 3803-3804).

Strominger teaches L-alanine (page 3804), which is a fragment of FXI, corresponding to either S434A or T475A. Please note, the specification does not define fragment, and thus a single amino acid residue is a fragment and inherently lacks the terminal amino acids.

Claims 104, 105, 108 and 109 are rejected under 35 U.S.C. 102(e) as being anticipated by WANG (US Patent 6,608,026 B1).

Wang teaches Ala-Leu-Pro (Table 4, column 20), which corresponds to a fragment of SEQ ID NO:15 (aa 482-484, Cys-Leu-Pro) where the fragment has a mutation corresponding to position C482S and inherently lacks the terminal amino acids.

Conclusion

NO CLAIMS ARE ALLOWED.

The prior art made of record on the attached PTO-892 and not relied upon in any rejection is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andrew D. Kosar whose telephone number is (571)272-0913. The examiner can normally be reached on Monday - Friday 8am-430pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571)272-0974. The fax phone number for the organization where this application or proceeding is assigned is (571)273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Andrew D. Kosar, Ph.D.
Art Unit 1654

ANISH GUPTA
PRIMARY EXAMINER